



Editorial Review

Diagnosis of pancreatic insufficiency in cystic fibrosis – a practical approach

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ABSTRACT

In many cystic fibrosis (CF) centers, consultation from gastroenterologist, are not routinely taken. Yet the original name 'cystic fibrosis of the pancreas' illustrates the importance of the digestive system in this disease. Nutritional status, occurrence of CF related diabetes, liver involvement, morbidity and mortality are largely associated with pancreatic function. Treatment depends on treating associated conditions as well. Knowledge of exocrine pancreatic function, sufficiency or insufficiency, is therefore paramount from diagnosis on. At present the best test for this purpose is determination of fecal elastase-1, which should therefore be used in clinical practice as the compulsory companion of a positive sweat test.

Key words: Cystic Fibrosis, pancreatic function, pancreas insufficiency, Fecal elastase-1

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INTRODUCTION

Cystic Fibrosis (CF) is in clinical practice erroneously often regarded as an exclusively pulmonary disease because much of the associated morbidity and mortality are related to pulmonary complications.^{1,2} This attitude not only reflects little clinical experience with the disease but reinforces the growing nasty habit not to include systematically a (pediatric) gastroenterologist in a CF team. Looking back on the original discovery of CF shows that it all started from the pancreas.

In 1938 an American pathologist described her findings in the pancreas of young children, dead from extreme under nutrition caused by chronic malabsorption.³ Under her microscope the pancreas was full of small cysts filled with sticky mucus, surrounded by fibrous scar tissue. The new entity was therefore called "cystic fibrosis of the pancreas". The pathology image perfectly explains these children's past clinical history.⁴

Normal pancreatic acini produce juice with digestive enzymes that is pushed on towards the duodenum. In CF however the pancreatic duct is obstructed by the sticky mucus and the acini are blown up to cysts. In an attempt to protect the surrounding tissue forms fibrotic scars. The enzymes for digestion of fat, protein and starch do not reach their site of action, the intestinal lumen, and as a result these nutrients are not absorbed and pass

largely unchanged in the stools which become voluminous, pale, greasy and malodorous. The child thus neither receives materials nor energy to develop and function. It fails to thrive, does not grow and has a typical malabsorption profile (skinny, thin limbs and massively blown belly).⁵ Their muscles are weak like their resistance and at the first serious infection, they succumb. This natural history illustrates that originally the disease was purely digestive and it was thought that the fatal character was the result of the extreme malnutrition. Only once these children survived the first months and years of nutritional ordeal it became obvious that they also developed a specific primary respiratory disease.

On the other hand once the sweat test had been developed as a diagnostic tool, some children with a positive sweat test were found to show little digestive problems. Their stools, growth, weight gain was almost normal and pancreatic function was only somewhat decreased. In contrast to the first group who was called pancreatic insufficient (PI) these ones were termed pancreatic sufficient (PS).^{3,5} In the years after initial diagnosis of exocrine pancreatic sufficiency the pancreas function can decline and a PS patient can irreversibly become PI. In a 5 year follow up period of a cohort of 184 CF patients Walkowiak et al.⁶ reported a decline in pancreatic function in 8/35 PS patients

who were eventually diagnosed as PI. A decline in pancreatic function is seen more frequently in infants than older patients.⁶⁻⁸

PANCREATIC FUNCTION AND CLINICAL MANIFESTATIONS

The difference in pancreatic function has tremendous consequences for treatment and prognosis. In order to obtain a normal growth and weight, nutrition for PI patients should always be much richer in energy and thus in fat.^{5,9,10} This can only be absorbed when large quantities of pancreatic enzymes are ingested with every meal.^{5,11} These nutritional commitments can put a high burden on patient and family because weight can become an obsession. Nightmares are populated by words like “calories, BMI, fat, weight, eat” while PS patients hardly know their meaning.¹²⁻¹⁴ PS patients are remarkably different: as problems start later, most are somewhat older at diagnosis. They spontaneously grow, take weight and develop rather well, have less and milder exacerbations, a better survival and quality of life.¹⁵ In the early nineties PS were found to survive about 20 years longer than PI. Was this just a result of the absence of malabsorption? The answer came about 25 years ago at the time of the description of the genotypes.¹⁶ More than 1500 different were discovered which could be divided into severe or mild on the basis of their correlation to clinical course, prognosis but also pancreatic function. In contrast to PS, severe were most common in PI. However, according to Bradley et al.¹⁷ other genes than the CFTR one may play a role in the BMI variation.

Other clinical manifestations are also associated with the pancreatic function. Meconium ileus is an exclusivity of PI. Problems with the handling of blood sugar mainly result from strangulation of insulin producing tissue in the pancreas by fibrotic scars and thus CF related diabetes is rarely seen in PS¹⁸ patients. This is important since untreated diabetes can cost several years of life. Liver disease is also mainly seen in PI patients.¹⁹ Early screening for this complication is thus less important in PS.

In summary, the difference in pancreatic function has important consequences. PI patients are at risk for malabsorption causing under nutrition and multiple deficiencies. They need lifelong nutritional counseling also on the importance of pancreatic enzyme replacement therapy. Even then they are not free of abdominal problems and a good weight gain and growth cannot be taken for granted. They are prone to develop diabetes and liver disease.

Respiratory evolution also needs to be followed closer because exacerbations are more frequent and more severe.

This package of dazzling complications leaves no doubt that it is essential to have information on the pancreatic function of every patient. That this is not self evident is illustrated by the fact that, according to a patient registry in the United States in 2005 only less than 15% of all CF patients ever had their pancreatic function investigated. As a result erroneous pancreas enzyme replacement therapy was very frequent: in a large group of 1200 patients 2% of the PI did not receive it and were thus at risk for

debilitating under nutrition while it was superfluously administered to 54% of the PS.²⁰ The latter is not dangerous but besides a waste of money, a needless charge to patients. Better results can easily be obtained since no complicated study's are needed just a yes-no answer to the question “is the patient pancreatic insufficient and thus in need of pancreatic enzyme replacement therapy?”

In the classically diagnosed infants who come to the doctor because of early complains the history and clinical presentation can already give indications on the digestive capacity. The pancreatic damage in cystic fibrosis already starts early in pregnancy and thus PI patients can already show subtle feeding problems from shortly after birth: despite a voracious appetite they fail to gain weight and produce large volumes of pale, yellow orange, greasy mal odorous stools. Soon they develop the typical malabsorption profile with protuberant belly. Closely watching growth and weight is essential because in retrospect the difference between PI and PS can often be read from the curves.²¹ PI CF infants with this presentation obviously come to the consultation earlier and are mostly earlier diagnosed than the PS without any early complaint. This clinical story mostly forms the key to pancreatic enzyme replacement therapy. Misconceptions are however common. The decision for lifelong enzyme replacement is too important to be only based on clinical impressions.²⁰ In every patient there is an absolute need to substantiate it by the objective evidence of a biochemical test. This is certainly true in the case of diagnosis by neonatal screening where clinical abnormalities are absent.

The scientific gold standard for biochemical tests²² is the direct measurement of enzymes in aspirated duodenal juice after the pancreas has been stimulated by the intravenous injection of two hormones, secretin and cholecystokinin (CCK). Although this secretine-CCK test is scientifically the most reliable it is in practice little performed in this young age group because it is not well standardized for infants and requires intestinal intubation, a rather invasive procedure. It is thus mainly reserved for scientific research and preference is given to the less invasive indirect tests.²³ These can be divided into 3 categories: the first measures the amount of undigested nutrients in the stools. In clinical practice the most popular test is the 72 hour faecal fat balance study. It calculates the fat absorption coefficient over 3 days from measuring the amount of fat in a 72 hour stool collection and relating it to the fat ingested over that period. It can be very accurate but defects in the completeness of the stool collection, the correct reporting of the ingested fat which has to be very high, the wide range of reported results and the distasteful character of the material make it mainly used for scientific work.

The tests of the second group measure compounds from special products split up by pancreatic enzymes, in blood, urine or exhaled breath. Especially the detection of C13 in exhaled air after ingestion of marked triglycerides gives an excellent result but its practical realization requires special, expensive equipment and collection of the material can be difficult in infants.

The third group of tests consists of direct measurements of pancreatic enzymes or derivatives in blood or stools. Those specific for the pancreas and performable on stool samples are preferred. Several candidates are valid but faecal elastase 1 stands out above all others.²⁴

It is a specifically human pancreatic protease discharged in the bowel if at least the pancreatic duct is open, which is not the case in PI CF people. It is not degraded during its passage through the intestine and is even somewhat concentrated in the colon. During diarrhea dilution can thus make the result abnormally low. It is stable for several days at room temperature and can thus easily be transported to a central laboratory for examination. As the test distinguishes human elastase from porcine in the pancreatic enzyme preparation, it can be performed when the replacement therapy has already been started. The distinction between PI and PS is mostly easy because the concentrations in the first are mostly far below 50 µg/g stools while in the PS they are in the lower range of normal's, above 200 µg/g stools. In young PS CF children it is appropriate to repeat it whenever new symptoms cast doubt or systematically every year until the age of about 5 years because it can change in that group.⁶ This test is at this moment undoubtedly the most easy and most reliable for clinical use, with an excellent correlation to direct and other indirect tests.²⁵

It should therefore be used in clinical practice as the compulsory companion of a positive sweat test in order to know soon after diagnosis whether therapy should include nutritional counseling and pancreatic enzyme replacement. Only in that way can a diagnosis be regarded as fully conclusive.

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